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Biliverdin Reductase Isozymes in Metabolism

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Abstract

Biliverdin reductase (BVR) isozymes, BVRA and BVRB, are cell surface membrane receptors with pleiotropic functions. This review compares, for the first time, the structural and functional differences of the isozymes. They reduce biliverdin, a byproduct of heme catabolism, to bilirubin, display kinase activity and BVRA, but not BVRB, can act as a transcription factor. The binding motifs present in the BVR isozymes allow for a wide range of interactions with components of metabolically important signaling pathways, such as with the insulin receptor kinase cascades, protein kinase, and inflammatory mediators. In addition, serum bilirubin levels have been negatively associated with abdominal obesity and hypertriglyceridemia. We will discuss the roles of the BVR isozymes in metabolism, and their potential as therapeutic targets.

Keywords

Biliverdin Reductase; BVRB; BVRA; Bilirubin; Heme Oxygenase; Obesity; Diabetes

Introduction

In obese individuals, adipocyte expansion leads to increased inflammation as a result of elevated proinflammatory molecule secretion from adipose tissue, which leads to an exacerbated oxidative state that contributes to adipocyte hypertrophy (1). Antioxidants may prove useful for reducing reactive oxygen species (ROS), preventing adipocyte expansion

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and chronic inflammation. Several studies have shown that activation of the heme oxgenase (HO) system reduces ROS, body weight, and blood glucose levels (2–7). HO catabolizes heme to produce carbon monoxide (CO), iron, and the tetrapyrrolic bile pigment biliverdin, which is further reduced to the antioxidant bilirubin, by the enzyme biliverdin reductase (BVR). Recent studies have demonstrated that BVR, through production of bilirubin as well as direct signaling, may interact with the insulin receptor and thus affect insulin signaling (8), whereas serum total bilirubin levels have been negatively associated with hypertriglyceridemia and abdominal obesity (9). However, the pathways by which BVR and its end product bilirubin signal in tissues like adipose and liver to help prevent insulin resistance and obesity are not well understood. Herein, we will discuss interactions and signaling pathways of the BVR system and its novel role as a metabolic regulator.

BVR isozymes; the basics

Structure and function

Specific structural sites of BVRA allow for the modulation of a diverse set of signaling pathways (Figure 1). The structure of BVRA can be divided into two major regions, the catalytic and the regulatory/DNA interaction domains. The N-terminus of BVRB and BVRA contains the catalytic domain and houses a binding motif for NADP(H) and NAD(H) cofactors (10). The C-terminus of BVRA encompasses the domain structures for the basic-leucine-zipper (bZiP) to function as a transcription factor, as well as the nuclear location sequence (NLS) and nuclear export sequences (NES) that are required for translocation into the nucleus and binding to regulatory regions of DNA (11, 12). However, these structures are absent in BVRB suggesting that this protein may not function in the same capacity as BVRA. The bZip site on BVRA has been shown to bind activating transcription factor-2 (ATF-2), which is known to regulate cAMP response elements (CRE) to increase the expression of a variety of genes, including c-jun, (13–17). The NLS and NES are also necessary for BVRA-facilitated movement of various signaling components, such as interaction with ERK (18), as well as binding to transcription regulators (14, 19). The SH2 binding motif on the C-terminus is associated with the insulin receptor kinase (IRK) signaling, allowing it to modulate insulin dependent pathways (20), discussed in detail below. The C-Box and D-Box domains serve as binding sites for various kinases in the mitogen activated protein kinase (MAPK) pathway and are important in the BVRA regulation of MEK (MAPK-ERK kinase)-ERK-ELK (eukaryotic-like protein kinase) signaling (18).

BVRA has the ability to bind DNA sequences such as the antioxidant response element (ARE) and hypoxia response elements (HRE) (11), which are bound by the bZip transcription factors, including NF-E2-related factor (Nrf2) (21, 22). Nrf2 proteins are known to be involved in combating oxidative stress and increasing the expression of HO-1 (23). It has also been shown that abrogation of the Nrf-2/ARE pathway leads to increased oxidative damage, which attenuates the ability to recover from hypoxia and apoptosis in mice (22, 24). Whether the BVRB isoform can also bind directly to DNA and activate similar response elements in genes is not know. However, given the structural differences

between the BVRA and BVRB proteins, it is unlikely that BVRB acts as a transcription factor.

Developmental profile

BVRB can be identified beginning at 14–15 weeks of human development, whereas BVRA expression increases closer to 20 weeks in gestation (25). BVRB remains present in all tissues into adulthood; however, its functional role is not known. BVRA is ubiquitously expressed in adult tissue with expression levels higher in brain and lungs as compared to tissues such as liver and placenta (26). The functional differences between BVR isozymes begin with their reduction specificity. BVRA reduces biliverdin IXα to bilirubin IXα, whereas BVRB reduces biliverdin IXβ to bilirubin IXβ (25, 27). HO cleaves fetal heme at the β-meso position producing biliverdin IXβ, whereas adult heme is predominately constructed to biliverdin IXα. An important advantage of bilirubin IXβ is its higher solubility that allows for its excretion in the absence of any type of conjugation, which is required for excretion of bilirubin IXα (28). During the early stages of development, fetal heme is the primary heme present within circulation. The use of BVRB in early maturation allows for the removal of biliverdin metabolites that would otherwise accumulate in high concentrations leading to toxic conditions in the developing fetus (27). To make bilirubin IXα soluble requires conjugation with glucuronic acid, which is driven by UDP-glucuronyltransferase (UGT1A1), an enzyme that is only present after the first week of birth (25). Bilirubin IXα is the major metabolite that is correlated with a reduction in obesity and increased during weight loss. The signaling involvement of the different bilirubin isotypes are unknown, but known structural similarities and differences in BVRA and BVRB (Box 1) may suggest that they have diverse functions.

BVR and Bilirubin in Metabolic Disorders

Along with being a potent antioxidant, bilirubin may also play a key role in obesity. Bilirubin can easily diffuse into the lipid environment (29), and moderately elevated plasma levels of bilirubin are associated with decreased abdominal obesity and lowered risk of metabolic syndrome (Figure 2) (30). This correlated with the observation that obese patients with elevated insulin and visceral adiposity have decreased levels of plasma total bilirubin (31). Patients with elevated plasma bilirubin also had increased adiponectin levels in blood, an anti-inflammatory cytokine directly secreted from adipose tissue (32). Andersson et al. investigated short-term weight loss in obese high-risk cardiovascular patients and found that plasma total bilirubin concentration increases as body weight decreases (33). It was recently shown that cobalt-protoporphyrin (CoPP) induction of HO and increased production of bilirubin in obese mice resulted in the elevation of peroxisome proliferator-activated receptor alpha (PPARα) expression and gene-regulatory activity, thus increasing fatty acid oxidation and amelioration of fatty liver development, and reduced body weight and blood glucose (2). In addition, CoPP and bilirubin treatments have been recently reported to increase insulin sensitivity and glucose tolerance in leptin-receptor deficient and in diet-induced obese mice through suppression of endoplasmic reticulum stress (34). However, it must be noted that whether CoPP acts solely through induction of HO-1 or through indirect effects of protoporphyrins on other heme containing proteins is not clear (35). There is also

the possibility that increased HO activity may increase signaling through biliverdin to the BVR enzyme to increase production of bilirubin which has in its own right the capacity to prevent diabetes and obesity. This hypothesis is supported by a recent study that demonstrated that BVR protects against glucose intolerance and diabetes by affecting the pancreatic islet. Treatment of rat pancreata with mesobiliverdin IXκ, a biliverdin IXκ analog that acts as a substrate for BVR, increased the yield of functional pancreatic islets; and transplantation of these islets into diabetic rats lowered blood glucose levels and reversed insulin dysfunction in diabetic rats (36). This study suggests an important role for intercellular generation of bilirubin in protection against diabetes and highlights the clinical potential of biliverdin analogs in protecting islets during allograft transplantation; however, specific studies in which intracellular bilirubin generation is decreased via knockout of the BVR isozymes are needed to fully elucidate the protective role of this pathway in metabolic disorders such as diabetes.

Biliverdin Reductase and Insulin Signaling Pathways

The most important mediator of metabolic processes is insulin, which is secreted after feeding from the pancreatic beta islet cells to initiate signal transduction pathways that increase glucose and fatty acid uptake by insulin responsive tissues. In non-insulin dependent diabetic patients, these processes become resistant in peripheral organs and result in insulin and glucose intolerance. Insulin causes autophosphorylation of tyrosine residues in the cytoplasmic portion of the transmembrane insulin receptor that phosphorylates insulin receptor substrate 1 (IRS-1) in tyrosine residues and activates IRK signaling pathways. The insulin signaling cascade diverges into two major arms, the PI3-kinase/Akt, and the IRK/IRS/PI3-kinase/MAPK pathway. BVRA but not BVRB is known to interact with components in both pathways, and thus may have a role in the regulation of metabolic processes (Figure 3) (8, 18).

PI3-kinase/Akt

Insulin stimulation of the PI3K pathway leads to downstream phosphorylation events that include the insulin kinase cascade (IRK), and Akt signaling pathways, known regulators of glucose uptake and energy storage (37). Phosphorylation of Akt (pAkt) modulates downstream targets that enhance glucose uptake via increased expression and translocation of glucose transporters (e.g. Glut4) to the cellular membrane, and positively effect glucose uptake through this pathway (Figure 3) (38). For these reasons, the PI3K/Akt axis has been a major target for drug development for insulin resistant and type II diabetes. BVRA has been shown to interact with several components of the IRK signaling cascade which make it a potential target for the treatment of type II diabetes. BVRB does contain a similar insulin receptor-interaction domain as BVRA, but whether BVRB can influence insulin signaling is not currently known. Most of what is known about the kinase activity function of BVRA and its involvement in insulin signaling has been pioneered by the Maines laboratory (8, 20), but the interaction between BVRA and PI3K has also been reported by other independent laboratories (39, 40). The effect of BVRA on insulin signaling remains controversial. There have been conflicting reports on BVRA and insulin signaling. Initial studies showed that siRNA suppression of BVRA enhanced glucose uptake in 293A embryonal human kidney

cells by decreasing serine phosphorylation of IRS-1(20). However, later investigations showed that siRNA suppression of BVRA increased pAkt in HK-2 proximal tubule epithelial human cells (41), human macrophages (40) and rat heart H9c2 cells (39), suggesting that BVRA may positively affect glucose uptake. The duality of BVRA on insulin signaling was further highlighted in a recent study using different peptide sequences of BVRA (8). The terminal ^{290}KYCCSRK peptide was found to increase glucose uptake and potentiate insulin, while a peptide (^{194}KEDQYMKMTV) corresponding to BVRA's SH2-binding domain was a potent inhibitor of glucose uptake and insulin signaling (8). This highlights the importance of the BVRA-PI3K interaction, and recommends that inhibition is detrimental to glucose uptake and possibly translocation of Glut4 to the cellular membrane (Figure 3). It appears that differences in response between the two peptides is due to where each of them targets the IRK signaling cascade (8). The differential effects exhibited by these BVRA peptides make them potential candidates for drugs targeting disorders of glucose metabolism especially type II diabetes. It is now apparent that not only is BVRA mediating bilirubin production, a potential therapeutic target for diabetes, but BVRA peptides could also be novel targets for the treatment of diabetes (Figure 3).

The PI3K pathway plays an essential role in protection from oxidative damage and serves as a cytoprotectant (42). Several mechanistic connections exist between the PI3K pathway and BVR, as it has been shown that BVR can link and activate the PI3K as well as the MAPK (Box 2) pathway arms of the IRK signaling pathway (20, 50). In addition, the human enzyme may function as an ERK nuclear transporter and ERK activator (50).

BVR can also protect from oxidative damage by regulation of HO-1 expression, as well as generation of bilirubin, a powerful antioxidant. Several studies have shown that reduction of BVRA protein via siRNAs leads to an increase in ROS levels (11, 43–46). BVRA has also been shown to increase HO-2 levels in cardiomyocytes, most likely via a decrease in HO-2 turnover, which allows for increased cardiac protection and decreased cardiomyocyte apoptosis, possibly through decreases in levels of ROS (47), and by activation of PI3K.

The PI3K pathway is inhibited by phosphatase and tensin homolog (PTEN), that catalyzes the dephosporylation of 3-phosphoinositide (PIP_3) to 2-phosphoinositide (PIP_2) (48) resulting in inhibition of the Akt signaling pathway. PTEN has been shown to be important for suppression of growth (49), and a reduction in PTEN leads to exacerbated Akt guided proliferation (37). Furthermore, inhibition of PTEN expression increases Akt phosphorylation, reversing insulin and glucose intolerance (50). It will be of interest to investigate if BVR isozymes can interact with the PTEN protein and/or promoter and if this interaction leads to increased PI3K signaling and attenuation of oxidative damage.

IRK/IRS/PI3-kinase

Insulin receptor activation leads to phosphorylation tyrosines and activation of IRS-1. However, interaction with c-Jun N-terminal kinase (JNK) or PKC results in phosphorylation of serines that is inhibitory to IRS-1 and IRK (20, 51–53). It has been shown that both the tyrosine and the serine/threonine kinase activities of BVR may contribute to insulin action and glucose uptake. BVRA was identified to contain a Y^{198}MKM sequence that functions as the binding site for proteins with Src homology 2 (SH-2) domains, such as in PI3K (20). The

four acidic residues YMXM in the N-terminus of BVR are also found in IRS, a feature frequently associated with tyrosine residues that are known substrates for protein tyrosine kinases (PTK) (20). BVRA has been shown to be a substrate for the insulin receptor, and a protein kinase for IRS-1 (Figure 3) (20). Three of the six-tyrosine residues (Y198, Y228, and Y291) in BVRA have been identified as targets for IRK-mediated phosphorylation, whereas tyrosines 72 and 83 are autophosphorylated (20). Tyrosine 198 in BVRA is the major target of IRK phosphorylation, and a mutation at this site enhanced glucose uptake, in 293A cells (20). The N-terminal serine/threonine kinase domain in BVRA contains an ATP-binding site at the G17 position that was shown to be responsible for phosphorylation of IRS-1 on serine residues (20). IRS-1 phosphorylation of proximal serines inhibits function and promotes insulin resistance (54, 55) and IRS-1 phosphorylation mutant analysis has revealed that serines 307, 312, 315, and 616 are all possible kinase targets of BVRA, implicating the enzyme in the control of IRS-1 function. Oxidative stress caused by tert-butylhydroperoxide (tBHP) robustly induced IRS-1 S616 phosphorylation in chondrocytes (56), suggesting that BVRA may enhance phosphorylation of S616 site in response to oxidative stress. However, this is yet to be shown. The BVRA-PI3K interaction may lead to the enhancement of IRS-1 S616 phosphorylation due to the direct effect of BVRA kinase activation on PI3K. As most of these findings are based on in vitro experiments, it is still unclear what is the involvement of the BVR isozymes in insulin signaling in relevant tissues in vivo, or their precise role in insulin resistance and diabetes, in the context of the whole organism. The generation of rodent model where the expression of the BVR isozymes is manipulated will help determine their function in insulin responsive tissues,.

Biliverdin Reductase Regulation of Protein Kinase Family

The protein kinase (PK) family regulates metabolic processes that include insulin actions on carbohydrate and fat metabolism, in muscle and adipose tissues, and lipid synthesis in liver. The PKA isoforms are important for lipolytic actions in adipose and inhibition of insulin signaling whereas the PKC class of serine/threonine kinases have diverse functions. BVRA is both a substrate and activator of PKCβII, via phosphorylation and protein-protein interactions (57). PKCβII may regulate insulin resistance through interaction with IRS-1 and the insulin-signaling pathway (58). PKCβII expression and activation, but not PKCα, are elevated in the fat tissues of diabetic ob/ob mice and in high-fat diet-fed mice, compared to lean animals (58). BVRA enhances PKCβII localization at the cellular membrane and is subsequently phosphorylated (57). Palmitate-induction of the super-oxide generating enzyme, Nox2, which forms ROS, was dependent on the activation of classical PKCs, specifically PKCβII (59). The BVRA and PKCβII interaction may be a sensor for palmitic acid induced ROS that occurs in fat accumulation in obesity. Also, BVRA may potentially inhibit PKCβII actions in adipocytes of obese patients to prevent the accumulation of ROS and activation of Nox2. Investigating the expression, localization and action of BVRA in the obese in the future is warranted.

BVRA also modulates PKCδ, a novel PKC involved in the regulation of cellular growth, survival, antigen presentation, and various cancers (60). PKCδ and BVRA share a number of common activators including ROS, IGF-1, and insulin. Multiple BVRA sites have been examined including the D (δ)-Box like motif, which most likely physically interacts to

increase the potency of the PKCδ catalytic domain (60). Suppression of BVRA expression has been shown to attenuate PKCδ mediated activation of NF-κB and Elk1, a discovery that could lend to inhibition of PKCδ mediated cancer proliferation (60). The ability of PKCδ to modulate BVRA in such a manner allows for its causal significance in many downstream effects linked to BVRA activity (45). The BVR substrate biliverdin is also a known inhibitor of PKCδ. Therefore, the reduction of biliverdin by BVR may alter PKCδ activity (60). It is unlikely that BVRB directly regulates PKC since it lacks the D (δ)-Box like motif; however, the regulation of PKC by BVRB has yet to be examined.

BVRA also interacts with PKCζ, an atypical PKC linked to TNF-α and NF-κB activity, effecting cellular growth and differentiation (61). BVRA and PKCζ share common activators and substrates; both have modulatory effects on the insulin/PI3K pathway, and have the ability to phosphorylate IRS-1, allowing for negative feedback (61). BVRA potentiates the activation of PKCζ by TNFα, a process likely involving sulfide bonds between the cysteine rich carboxyl terminal of BVR and cysteine rich regions of PKCζ (61). Studies have shown that BVRA peptide fragments have the ability to decrease the activity of PKC, a process that could be useful for the treatment involving excessive cellular growth and cancer proliferation (60, 61), as well as metabolic disorders. PKCθ also regulates IRS-1 (62); however, the BVRA-PKCθ interaction is yet to be investigated.

Biliverdin Reductase Regulation of Inflammatory Pathways

The autophosphorylation of specific serine/threonine residues stimulates the reductase activity of BVRA (20). Phosphorylated BVRA regulates the expression of oxidative-stress-responsive genes such as HO-1 or inducible nitric oxide synthase (iNOS) and interacts with members of the MAPK kinase family, including ERK1/2 (11, 63, 64). These effects highlight BVRA as one of the early events in adaptive response to stress, which has the capability to reduce ROS-induced damage and reduce inflammation. ROS enhances activity of the major mediator of inflammation, NF-kB, which then increases expression of proinflammatory genes, such as TNFα, and enhances the proliferation of immune cells. TNFα, which is increased in obese individuals, promotes infiltration of immune cells in adipose and liver leading to a chronic inflammatory state and insulin resistance (65). BVR is expressed on the surface of macrophages. In the context of a lipopolysaccharide (known activator of TNFα (66)) induced inflammatory response, BVR surface expression and phosphorylation is increasing, and through its kinase activity, BVR initiates an inflammatory response via the Akt/PI3K pathway and enhanced production of the anti-inflammatory cytokine interleukin-10 (IL-10) (40).

The interaction of pro- or anti- inflammatory molecules with the BVR isozymes and their signaling potential has yet to be specifically investigated. It is possible that differential signaling pathways could regulate the levels of BVRA and BVRB proteins and that each of the isozymes could have differential effects on inflammatory cytokine signaling. For example, BVRA recruitment to the cell surface in obese individuals may inhibit TNFα induced inflammation, reducing chronic inflammation and the accumulation of fat. Overall, the biliverdin IXα/BVRA axis inhibits ROS, preventing the increase of inflammatory

pathways, which may play a major role against pathways promoting insulin resistance and inflammation seen in obesity.

Concluding remarks and future perspectives

The diversity of functions associated with the BVR isozymes allows for their modulation of many downstream target molecules via protein-protein interaction, phosphorylation, and transcriptional regulation, which makes them potential targets for the development of new drugs in several areas including cardiovascular, metabolism and cancer. With regards to metabolism disorders, development of BVRA peptide agonists (8) could provide novel therapeutics for the treatment of type II diabetes. Also strategies to increase the levels of BVRA protein itself could be beneficial through increases in intracellular bilirubin generation as well as direct signaling through cytoprotective pathways such as IRK/IRS/PI3-kinase and PKC. In cancer, inhibition of the BVR isozymes could provide novel opportunities for the development of new chemotherapeutics as well as increase the efficacy of existing drugs. For example, it was shown that overexpression of BVRA was associated with increased protection from cisplatin and doxorubicin treatment in cultured cells (67). These results would indicate that specific targeting of BVRA could be a novel approach for the development of a whole new class of cancer chemotherapeutics. BVRB allows for the proper function of heme breakdown and metabolite removal in the early stages of fetal development. Apart from its role early in fetal life, functions for BVRB in adulthood are not known. Recent studies have shown BVRB levels to be significantly increased in both hepatocellular carcinoma and prostate cancer (68, 69), suggesting that inhibitors of BVRB could also be a new class of chemotherapeutic compounds. However, much research into the underlying mechanism(s) by which BVRB promotes cancer growth is needed. Future insights into the complex physiological roles for BVRA and BVRB will be derived mainly from studies in which the levels of each of these isoforms are altered using genetic approaches via infusion of siRNAs or creation of tissue-specific knockouts for each isozyme. It is possible as a result of this work that new and effective drugs for a wide-variety of disease could be based upon alterations in BVRA/BVRB signaling.

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BOX 1. Comparison of the BVR isozymes

The reduction of biliverdin to bilirubin was first characterized in 1936 by Lemberg and Wyndam (70). Later, Singleton and Laster purified the reducing enzyme, BVR, and demonstrated that the enzymatic reaction was specific for biliverdin (71). Today, BVR is known to be present as two major isozymes, BVRA and BVRB (72). The BVRA gene is on chromosome 19 at the q13.1–13.2 region, and BVRB is located on chromosome 7 at the p14 region (73, 74). Unique chromosomal locations suggest that BVRA and BVRB may have major differences in their structure and function; comparison of human BVRA to BVRB shows only an 11.3% identity (20.4% similarity) (Figure I). There is an 81.8% identity (91.9% similarity) between the human and mouse BVRA, and 93.2% identity (96.6% similarity) between the human and mouse BVRB, indicating that BVR function is conserved across species. However, their roles in reducing biliverdin vary throughout development.

BOX 2. BVRA and MAPK signaling crosstalk

The MAPK proteins are a group of kinases that consist of various subfamilies including ERK1/2, p38, and JNK. These kinases take part in one branch of the insulin-signaling pathway. ERK1/2 is activated by MEK1/2, which is regulated by BVRA, possibly by interaction with the PKC family (18, 75). BVRA contains two sites that are able to bind to ERK, one being the D-box docking site and the other being the FXFP site (18, 76). Potentially, this interaction is mediated by the C-terminal α-helix of BVRA, which is similar to the D-(δ) box/domain found in ERK1/2 and JNK substrates (18). BVRA allows for communication between cytosolic and downstream nuclear proteins, along with subsequent molecular and morphological changes dependent on these pathways. BVRA forms a ternary complex with MEK and ERK and helps to position ERK in the MEK-ERK complex, allowing for the activation of ERK by MEK (18) (Figure I). Once BVRA complexes with MEK and ERK, it transports the activated ERK into the nucleus, and the two proteins complex with Elk for further downstream activation and regulation of gene expression (18).

Highlights

- Biliverdin reductase isozymes are major regulators of metabolic processes.
- The BVR isozymes have structural differences that lead to variances in signaling.
- BVRA directly regulates insulin receptor signaling.
- Bilirubin treatments may function to prevent obesity and diabetes.

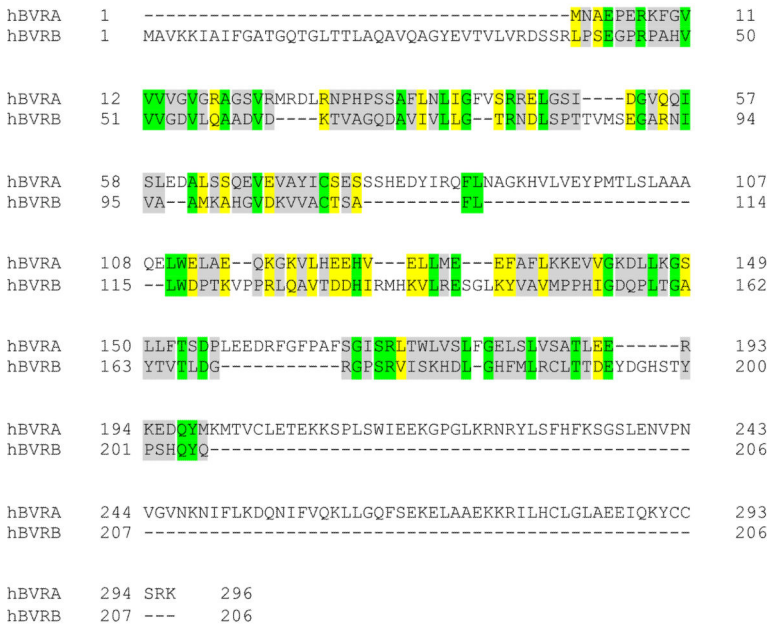

Figure I, Box 1. Alignment of human biliverdin reductase A and B isozymes

The alignment of BVRA and BVRB was done using the EMBOSS Pairwise Sequence Alignment (PROTEIN) software (https://www.ebi.ac.uk/Tools/psa/emboss_needle/). Identical regions are highlighted in green, similar regions are in yellow, and gray indicates no similarity between amino acid alignments.

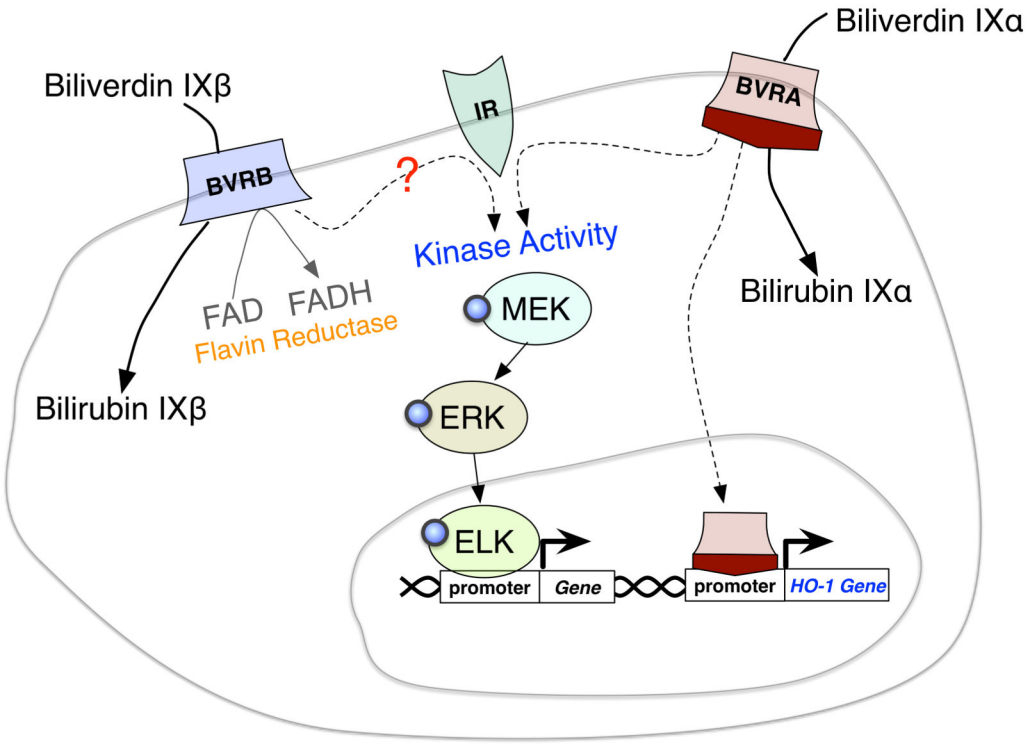

Figure II, Box 2. Diagram of the differences in biliverdin reductase A and B signaling and enzymatic activity

BVRA and BVRB reduce biliverdin to bilirubin via their BVR domain. BVRB reduces only biliverdin IXβ, and BVRA has only enzymatic activity on biliverdin IXα. BVRB also has the ability to reduce flavins (FAD to FADH). BVRA has been shown to interact directly with the insulin receptor (IR) and proteins involved in the IR signaling cascade (MEK, ERK, and ELK). BVRA can also directly bind to the promoter of genes, such as HO-1 and regulate transcription. BVRB cannot bind directly to DNA, but does contain the domain that BVRA has been shown to interact with IR, suggesting a potential role in insulin signaling.

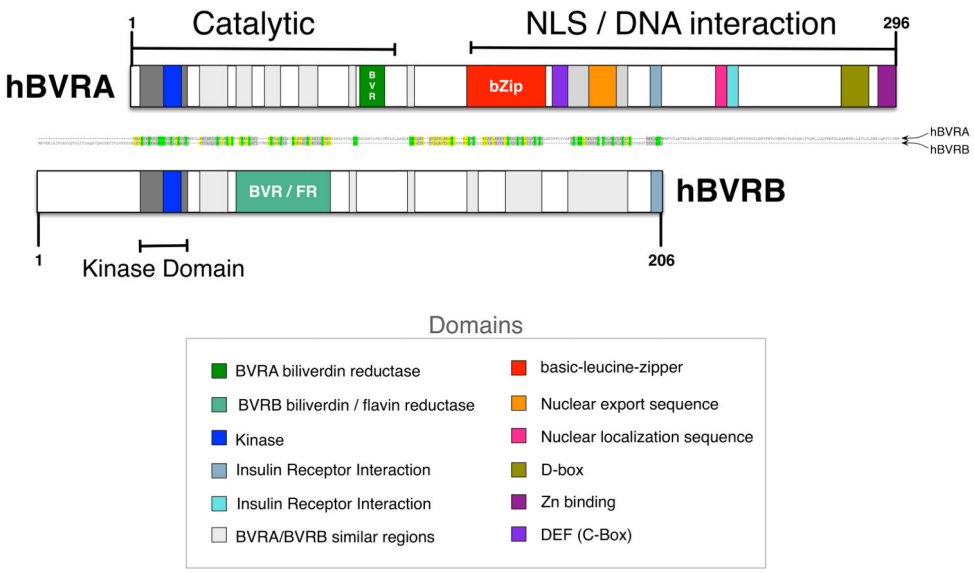

Figure 1. Domain structures of human biliverdin reductase A and B isozymes

Domain structural comparisons of BVRA and BVRB indicate that there is a similar kinase and catalytic domain for both isozymes. The major difference is in the C-terminus, where BVRA contains a bZip DNA binding domain, nuclear localization signaling, and nuclear export signal that are not located within BVRB.

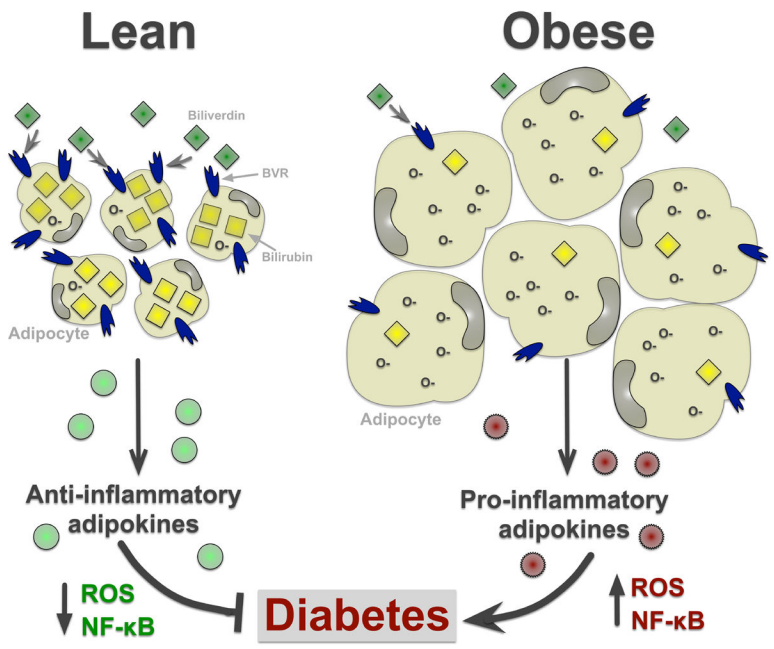

Figure 2. BVR and bilirubin levels and their association with obesity

Increasing plasma levels of bilirubin are associated with decreased adipocyte size by scavenging free radicals (O-) and increasing production of anti-inflammatory adipokines (e.g. adiponectin), thus lowering the risk of type II diabetes. Obese patients have decreased levels of plasma total bilirubin (31), which results in increased free radicals and ROS, and in the enhancement of NF-kB mediated inflammation. This leads to adipocyte hypertrophy and increased production of pro-inflammatory adipokines (e.g. TNFα) that contribute to diabetes.

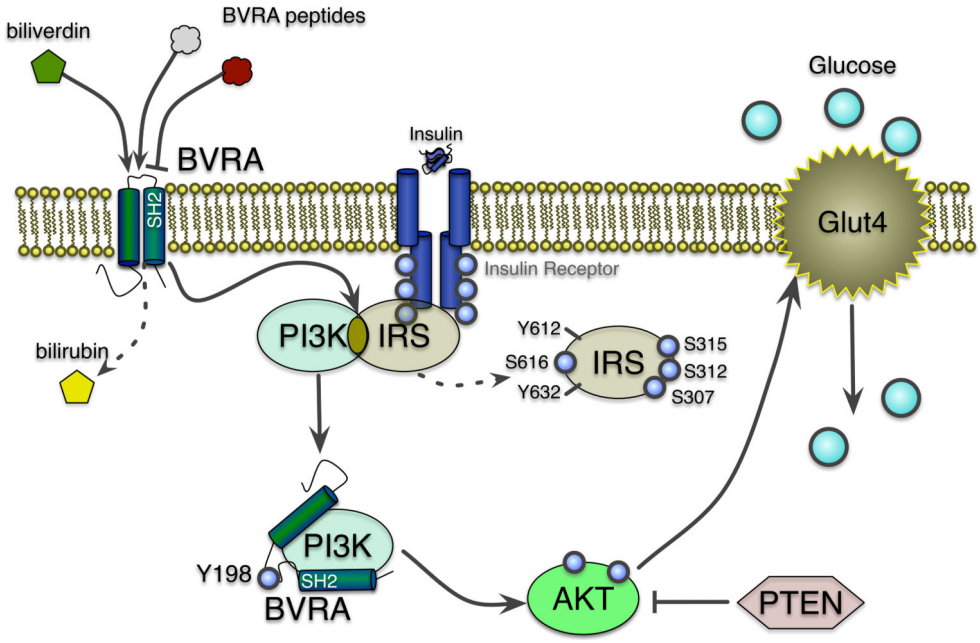

Figure 3. Involvement of BVRA in the insulin receptor signaling cascade

Activation of BVRA increases insulin receptor and PI3K signaling (39, 41), which enhances phosphorylation of Akt (8, 39, 41) and Glut4-mediated glucose uptake. BVRA inhibits the IRS-1 and PI3K interaction by phosphorylation of IRS-1. The serine 315 phosphorylation of IRS-1 uncouples it from the insulin receptor and inhibiting function (55). The SH2 domains in BVRA bind directly to PI3K to enhance pAkt signaling and glucose uptake (39–41). Biliverdin activation of BVRA increases pAkt and glucose uptake, while the BVRA peptides have inhibitory and stimulatory roles. The BVRA peptides that target the SH2-binding domain inhibits glucose uptake.